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EXAMINER	
CLARK, SARA E	

ART UNIT	PAPER NUMBER
4121	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/521,421	SCHARER ET AL.	
	Examiner	Art Unit	
	SARA E. CLARK	4121	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/25/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

NON-FINAL REJECTION

This is a 371 (national stage) application of PCT/CH03/00435, filed 7/2/2003, which claims priority to Swiss applications 0015/03, filed 1/8/2003; 1375/02, filed 8/8/2002, and 1242/02, filed 7/16/2002. Claims 1-21, as amended, are pending.

Priority

1. Applicant's claim to foreign priority is acknowledged. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. A review of the related applications indicates that the claims of the instant application are supported in the disclosure of Swiss application 1242/02, filed 7/16/2002. Therefore, amended claims 1-21 are entitled to an effective filing date of 7/2/2003, and a foreign priority date of 7/16/2002.

Information Disclosure Statement

2. All references submitted by Applicant on the IDS dated 4/25/2005 have been considered.

Claim Rejections - §112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 11 is rejected under 35 U.S.C. 112, second paragraph, for lack of an antecedent basis, rendering its meaning indefinite.

5. Claim 11 recites, in part, "the process of claim 1, characterized in that the compound of general formula (II) for the introduction of the Boc protecting group is Boc anhydride or Boc carbamate." A plain reading of this language suggests that *the compound of general formula (II)* is Boc anhydride or Boc carbamate, although this clearly would not result in the desired product of formula (I). Further, claim 1 recites Boc only as one option for R4, not as an essential element, and makes no reference to "the" Boc protecting group. The meaning of claim 11, therefore, cannot be reasonably interpreted.

6. Claim 16 is rejected under 35 U.S.C. 112, second paragraph, for lack of an antecedent basis, rendering its meaning indefinite. Claim 16 depends from claim 1, and recites "the quinine used in step B" of claim 1. However, claim 1 makes reference only to a benzoquinone, not quinine. Benzoquinones are a class of compounds of varying structure, whereas quinine is a single compound of defined structure that also does not belong to the class of benzoquinones. Therefore, Applicants' intent is unclear, such that claim 16 is insolubly ambiguous and cannot be interpreted in any meaningful way. See MPEP 2173.05(e).

7. Claims 20 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 20 recites, in part, "the resulting compound of the formula (I) . . . is crystallized in the polymorphic form I;" and claim 21 recites, in part, "the resulting compound of the formula (I) . . . is crystallized in the polymorphic form II." The specification discusses "polymorphic forms I and II" on p. 7, para. 25, but is silent

as to what structural attributes each polymorphic form has, their significance, or what distinguishes them from each other, aside from the fact that they recrystallize at different temperatures. While Applicants are free to be their own lexicographers, what constitutes "polymorphic forms I and II" of finasteride is not defined in the specification or in the literature relating to its synthesis, such that the metes and bounds of claims 20 and 21 cannot be understood by one of ordinary skill in the art.

Claim Rejections - §103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1-3, 5-7, 9, 12-14, and 16-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bhattacharya et al. (EP application no. 0 298 652, published 1/11/1989, provided by Applicant on the IDS dated 4/25/2005), in view of King et al. (US Pat. 5,091,534, issued 2/25/1992), and Tsuji et al. (Tetrahed. Lett. 25 (42), 4783-6 (1984), provided by Applicant on the IDS dated 4/25/2005).

Applicant admits in the specification (p. 5-6) that the claimed processes with the claimed compounds are known; claim 1 merely reframes these known procedures. Specifically, step (A) recites

- A1: starting with a 17β-substituted-3-oxo-4-aza-androstane of formula (II);

- A2: introducing protecting groups R_3 and R_4, both of which can be trialkylsilyl, onto the A-ring lactam C_3 carbonyl oxygen and N_4, respectively;
- A3: to yield the 17β-substituted-3-oxo-4-aza-androstane intermediate of formula (III).

Step (B) recites

- B1: reacting the intermediate of formula (III) with a benzoquinone;
- B2: in the presence of a dehydrogenation catalyst;
- B3: to form a double bond between C_1 and C_2 (Δ^1).

Finally, step (C) recites

- C1: removing the trialkylsilyl protecting groups R_3 and R_4 from the C_3 carbonyl oxygen and N_4, respectively;
- C2: to yield the 17β-substituted-3-oxo-4-aza- androst-1-ene corresponding to general formula (I).

Bhattacharya et al. (1989) teach a method of dehydrogenation of C_1 and C_2 to yield a double bond between them (Δ^1) with the following steps:

- starting with a 17β-substituted-3-oxo-4-aza-androstane corresponding to general formula (II) of claim 1 (page 4, lines 5-56);
- using bistrimethylsilyltrifluoroacetamide (BSTFA) to add a protecting silyl group to the A-ring lactam C_3 carbonyl oxygen (page 5, substructure (e)), and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to substitute a C_2 hydrogen with a benzoquinone moiety (page 9, lines 20-30);

- heating the mixture to dehydrogenate C_1, release the quinone moiety from C_2, and deprotect the C_3 carbonyl oxygen, forming a double bond between C_1 and C_2 (Δ^1) (p. 9, lines 20-48);
- yielding the 17β-substituted-3-oxo-4-aza- androst-1-ene corresponding to general formula (I) of claim 1 (page 8, lines 1-43).

In summary, Bhattacharya et al. teach steps A1, part of A2 (adding a trimethylsilyl protecting group to the C_3 carbonyl oxygen, corresponding to R_3), B1, B3, part of C1 (removing the R_3 trimethylsilyl protecting group from the C_3 carbonyl oxygen), step C2, and formulas (I) and (II) of the claimed invention. Because the method of Bhattacharya et al. does not require protection of N_4, some steps of the claimed invention are not taught; namely, parts of steps A2 and C1 (protecting and deprotecting N_4, respectively); step A3, in which an intermediate of formula (III) is formed; and step B2, which recites the use of a dehydrogenation catalyst.

However, King et al. teach a method of introducing a double bond between between C_1 and C_2 of a 17β-substituted-3-oxo-4-aza-androstane of formula (II) in which both the A-ring lactam C_3 carbonyl oxygen and N_4 are protected by the addition of trialkylsilyl groups to each (col. 3, lines 60-65), resulting in the formation of an intermediate corresponding to formula (III), which reads on steps A2 and A3 of the claimed invention. While deprotection of the C_3 carbonyl oxygen and N_4 is not a discrete step in the method of King et al., acid is used to extract the final product, which is the same unsilylated 17β-substituted-3-oxo-4-aza- androst-1-ene corresponding to formula (I) of claim 1. In other words, King et al. teach the synthesis of the product arrived at in

step C2, so the deprotection (desilylation) of step C1 occurs as part of the acid extraction process.

Bhattacharya et al. and King et al. teach the synthesis of 17β-substituted-3-oxo-4-aza-androst-1-enes from the corresponding saturated precursor without the use of a dehydrogenation catalyst. However, King et al. point out that the silylation method of introducing a C_1-C_2 double bond is generally applicable in the synthesis of α,β-unsaturated lactams. Indeed, Tsuji et al. (1984) teach the synthesis of α,β-unsaturated ketones, as in the A ring of formula (I), by dehydrogenating O-silylated (protected) ketene acetals with a palladium dehydrogenation catalyst (p. 4785), which reads on step B2 of claim 1.

Tsuji et al. found that the use of a palladium catalyst, such as $Pd(OAc)_2$, in a nitrile solvent is an efficient method for preparing α,β-unsaturated ketones (p. 4783), precisely the object of the claimed invention. King et al. observe that the use of a silylating reagent mediates substitution on the lactam ring at the α-methylene carbon (i.e., C_2), useful for making the Δ^1-olefin azasteroid derivatives known to have potent 5α-reductase inhibitory activity (col. 3, line 65 – col. 4, line 4).

Further, Bhattacharya et al. teach a wide array of 17β-substituents (corresponding to R in formulas I-III of the claimed invention) that are largely co-extensive with and can be nearly any of those defined in claim 1 (p. 5, line 55, to p. 6, line 45). Thus, the 17β-substituents of Bhattacharya et al. also include

- –C(O)-NH-tert-butyl (finasteride), which reads on claims 2 and 3;
- -C(O)-NH-CH_3, which reads on claim 5; and

- -C(O)-N-, where N is the heteroatom of a 5- to 6-membered saturated ring, which reads on the piperidine or pyrrolidine of claim 6.

Both Bhattacharya et al. and King et al. teach the trimethylsilylation of the C_3 carbonyl oxygen; i.e., the O-protecting group corresponding to R_3 is trimethylsilyl, which reads on claim 7. Bhattacharya et al. also teach the use of DDQ, a chloro- and cyano-substituted benzoquinone, which reads on claim 16, assuming the "quinine" recited therein was intended to be "benzoquinone." In addition, Bhattacharya et al. teach the compound of formula (I) in which the 17β-substituent is a hydroxyl group or the salt of an alkali metal (p. 6, line 15), which reads on claim 18. Finally, Bhattacharya et al. teach the crystallization of compounds of formula (I) from toluene, which reads on claim 19.

As noted above, Tsuji et al. teach the use of a palladium dehydrogenation catalyst, which reads on claim 12. Specifically, they teach the use of tris-(dibenzylidineacetone) dipalladium-chloroform complex ($Pd_2(dba)_3CHCl_3$) (p. 4784), which reads on claim 13; and $Pd(OAc)_2$, which reads on claim 14.

King et al. teach the trimethylsilylation of N_4; i.e., the N-protecting group corresponding to R_4 is trimethylsilyl, which reads on claim 9. King et al. also teach the use of acid to extract the final product (1N HCl in Example 4; acetic acid in Example 7), which reads on claim 17.

Therefore, in the conversion of a 17β-substituted-3-oxo-4-aza-androstane of formula (II) to a 17β-substituted-3-oxo-4-aza- androst-1-ene of formula (I) through a protected (N- and O-silylated) intermediate, as taught by King et al., using a benzoquinone to oxidize C_2 as taught by Bhattacharya et al., and a palladium

dehydrogenation catalyst to yield a double bond between C_1 and C_2 as taught by Tsuji et al., combining these methods into the same process for the efficient production of medically useful 17β-substituted-3-oxo-4-aza-androst-1-enes of formula (I) would have been obvious to a person of ordinary skill in the art at the time the invention was made.

10. Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bhattacharya et al., King et al., and Tsuji et al. as applied to claims 1-3, 5-7, 9, 12-14, and 16-19 above, and further in view of Rasmusson et al. (US Pat. 4,760,071, issued 7/26/1988).

Rasmusson et al. teach novel 5α-reductase inhibitors and processes for their preparation, specifically 17β-N-monosubstituted-carbamoyl-4-aza-5α-androsten-1-en-3-ones, corresponding to formula (I) of the claimed invention. The compounds of Rasmusson et al. include a –C(O)-NH-tert-butyl substituent at C_{17} (finasteride), which reads on claims 1-3; and a -C(O)-NH-2,5-bis(trifluoromethyl)phenyl substituent at C_{17} (dutasteride), which reads on claim 4 (col. 2, lines 25-46). The synthesis methods of Rasmusson et al. use benzeneseleninic anhydride under anhydrous conditions with a strong base, which is noted by Bhattacharya et al. and King et al. to present many drawbacks, which their methods address. Therefore, to use the methods of Bhattacharya et al. in combination with those of King et al., with the catalysts of Tsuji et al., to prepare the compounds of Rasmusson et al. would have been obvious to one skilled in the art at the time the invention was made.

11. Claims 1, 8, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bhattacharya et al., King et al., and Tsuji et al. as applied to claims 1-3, 5-7, 9, 12-14, and 16-19 above, and further in view of Wakselman (in *Encyclopedia of Reagents for Organic Synthesis*, 2001).

Wakselman teaches a method of adding tert-butyl-oxycarbonyl (Boc) protecting groups to the nitrogen of a cyclic lactam (equation 21), corresponding to the N-protecting group R_4, which reads on claim 8. The reagent taught by Wakselman to carry out the reaction is di-*t*-butyl dicarbonate (a.k.a. Boc anhydride), which reads on claim 11 (if it is interpreted to mean that Boc anhydride or Boc carbamate is the reagent used to add the Boc protecting group to the compound of formula II). Claim 1 recites that R_4 can be Boc or trialkylsilyl, both of which are removed by acid hydrolysis, such that by its own terms, the two are interchangeable as N-protective groups. Therefore, combining the methods of Bhattacharya et al. with those of King et al. and the catalysts of Tsuji et al., substituting the N_4-Boc protecting group of Wakselman for the N_4-trimethylsilyl protecting group of King et al., would have been obvious to one skilled in the art at the time the invention was made.

12. Claims 1 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bhattacharya et al., King et al., and Tsuji et al. as applied to claims 1-3, 5-7, 9, 12-14, and 16-19 above, and further in view of King et al. (EP app. No. 0 428 366, published 5/22/1991, provided by Applicant on the IDS dated 4/25/2005).

King et al. (1991) teaches a method of introducing a 1,2 double bond into

compounds corresponding to formula (II) of the claimed invention, using oxalyl chloride to produce an intermediate in which the O- and N-protecting groups cyclize (p. 4, lines 5-25). King et al. (1992) notes the efficiency of the reaction with acid chlorides generally (col. 3, lines 35-36), which include oxalyl (C_2), malonyl (C_3) and succinyl (C_4) chlorides. The close structural similarity of acid chlorides accounts for their similar properties, such that substituting malonyl chloride for oxalyl chloride as a reagent in a multi-step synthesis would not be expected to materially alter the product of the reaction. See MPEP 2144.09. Using malonyl chloride rather than oxalyl chloride to protect the C_3 carbonyl oxygen and N_4 and link them together corresponds to the embodiment of the claimed invention in which R_3 and R_4 are linked by $-C(O)-CH_2-C(O)-$, which reads on claims 1 and 10.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use an acid chloride to introduce the R_3-R_4 cyclic protective group, as taught by King et al. (1991), combined with the teachings of Bhattacharya et al., King et al. (1992), and Tsuji et al., to arrive at the cyclic intermediate recited in claims 1 and 10.

13. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bhattacharya et al., King et al., and Tsuji et al. as applied to claims 1-3, 5-7, 9, 12-14, and 16-19 above, and further in view of Blaser et al. (US Pat. 4,335,054, issued 6/15/1982).

Blaser et al. teach the use of 2-2,bipyridyl complexed with $Pd(OAc)_2$ for use as a palladium catalyst in the synthesis of alkenylbenzenecarboxylic acid derivatives (col. 6,

lines 60-68), which reads on claim 15. Complexing a metal catalyst with a stabilizing agent is a known technique for reducing reaction times and/or temperatures and/or to increase the reaction yield, such that its use in combination with the catalysts of Tsuji et al. and the methods of Bhattacharya et al. and King et al. would have been obvious to one skilled in the art at the time the invention was made.

Conclusion

14. Claims 1-21 are rejected.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARA E. CLARK whose telephone number is (571) 270-7672. The examiner can normally be reached on Monday - Thursday, 7:30 am - 5:00 pm (EST). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Patrick J. Nolan can be reached on 571-272-0847. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Sec

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